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# (54) Nucleic acid library arrays, methods for synthesizing them and methods for sequencing and sample screening using them

(57) Methods for discriminating between fully complementary hybrids and those that differ by one or more base pairs and libraries of unimolecular, double-stranded oligonucleotides on a solid support. In one embodiment, the present invention provides methods of using nuclease treatment to improve the quality of hybridization signals on high density oligonucleotide arrays. In another embodiment, the present invention provides methods of using ligation reactions to improve the quality of hybridization signals on high density oligonucleotide arrays. In yet another embodiment, the present invention provides libraries of unimolecular or intermolecular, double-stranded oligonucleotides on a solid support. These libraries are useful in pharmaceutical discovery for the screening of numerous biological samples for specific interactions between the double-stranded oligonucleotides, and peptides, proteins, drugs and RNA. In a related aspect, the present invention provides libraries of conformationally restricted probes on a solid support. The probes are restricted in their movement and flexibility using double-stranded oligonucleotides as scaffolding. The probes are also useful in various screening procedures associated with drug discovery and diagnosis. The present invention further provides methods for the preparation and screening of the above libraries.

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## Discrimination Using RNase A

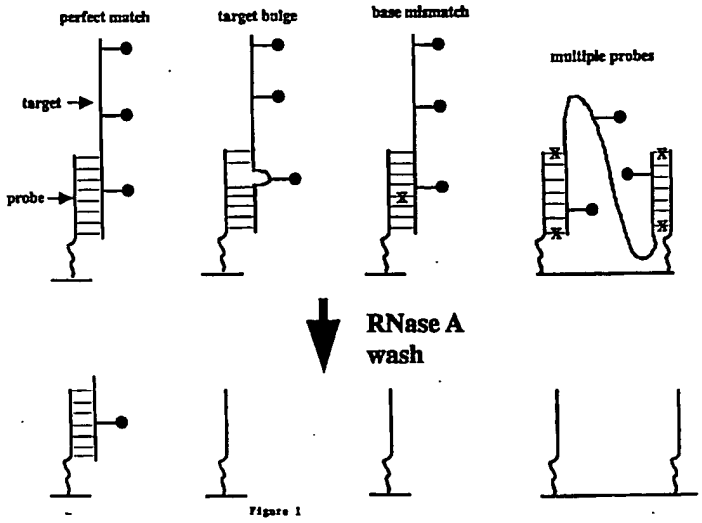


Figure 1

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# EUROPEAN SEARCH REPORT

Application Number
EP 95 30 7501

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TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C12Q

~~The present search report has been drawn up for all claims~~

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| THE HAGUE | 17 May 1999 | MOLINA GALAN E. |

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

European Patent Office

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Application Number
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## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int.Cl.6) |
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~~The present search report has been drawn up for all claims~~

| Place of search | Date of completion of the search | Examiner |
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| THE HAGUE | 17 May 1999 | MOLINA GALAN E. |

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Application Number
EP 95 30 7501

## CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

## LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☒ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

1-11

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## LACK OF UNITY OF INVENTION
## SHEET B

Application Number
EP 95 30 7501

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 1-11

   Methods for sequencing nucleic acids using oligonucleotide probe arrays or libraries.

2. Claims: 12-27

   Double-stranded unimolecular oligonucleotide libraries, methods for synthesizing or forming them and screening methods using them.

3. Claim : 28

   Oligonucleotide array based adhesives.

4. Claims: 29-32

   Intermolecular, doubly-anhored, double-stranded oligonucleotide library.

5. Claim : 33

   Method for preparing single stranded nucleic acid sequences.

## ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 95 30 7501

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